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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,632	11/25/1997	ELAZAR RABBANI	ENZ-53(C)	4638

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EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,632	RABBANI ET AL.	
	Examiner	Art Unit	
	Amy H. Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *246-252,255,257-260 and 264-270* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *246-252,255,257-260 and 264-270* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 November 1997* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 3/23/2006 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 9/23/2005 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 246-252, 255, 257-260 and 264-270 are pending in the instant application.

Applicant's amendments filed on 7/13/06 and/or arguments filed on 3/23/2006, with respect to the claim objections and rejection(s) under 35 U.S.C. 112, 2nd paragraph and 35 U.S.C. 102, have been fully considered and are persuasive. Therefore, the rejection has been withdrawn.

However, upon further consideration, a new ground(s) of rejection is made in view of the claim amendments filed on 7/13/2006.

Response to Arguments--Claim Rejections - 35 USC § 112, first paragraph

Claim 268 stands rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record set forth in the office action mailed on 9/23/2005. **This is a new matter rejection.**

Applicant asserts that there is support in the specification by way of illustration of examples in Figures 1-3 and Examples 1-4. However, the mere presences of figures that depict the presence of ligands in several positions does not offer specific support for "two or more", as instantly recited.

There does not appear to be specific support for a recitation of "two or more locations" within the context of the claimed invention. Should applicants disagree, applicants are invited to point out with specificity by page and line number where any such support may exist.

New Objections/Rejections

Claim Objections

Claim 266 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 266 recites is directed to the construct of claim 248, wherein said construct carries a net positive charge or a net negative charge, or is neutral or hydrophobic. Since there are no

alternatives other than positive, negative, or neutral charges, the claim fails to further limit claim 246.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 259 and 260 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 259 recites the limitation "The construct of claim 246, wherein said synthetic polymer..." However, claim 246 does not recite a synthetic polymer. There is insufficient antecedent basis for this limitation in the claim. Claim 260 is rejected because it depends from claim 259. Therefore, these claims were not further treated on the merits.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 246-252, 255, 257, 258 and 264-270 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. **THIS IS A NEW MATTER REJECTION.**

The instant claims are directed to a chemically modified nucleic acid construct, said construct comprising a modified nucleotide, a nucleotide analog, or a combination of the foregoing, wherein said modified nucleotide or nucleotide analog comprises a non-nucleic acid entity, "wherein said non-nucleic acid entity confers nuclease resistance, cell targeting, cellular localization or nuclear localization, or a combination of the foregoing".

The specification discloses that "non-nucleic acid entity or entities" include natural polymers, synthetic polymers, natural ligands and synthetic ligands, as well as combinations of any and all of the foregoing. When the non-nucleic acid entity or entities take the form of a natural polymer, suitable members may be modified or unmodified. Natural polymers can be selected from a polypeptide, a protein, a polysaccharide, a fatty acid, and a fatty acid ester as well as any and all combinations of the foregoing.

The amendment to claim 246 to recite "wherein said non-nucleic acid entity confers nuclease resistance, cell targeting, cellular localization or nuclear localization, or a combination of the foregoing" is new matter because the specification only teaches that chemical modifications or ligands can confers nuclease resistance, cell targeting, cellular localization or nuclear localization and does not teach that any "non-nucleic acid entity" or entities confer such results.

Applicant's arguments filed 3/23/2006 state that support for the amendments to claim 246 is supported by the specification on pages 31-47, more specifically on page

34 at lines 4-11 and 13-16. However, the paragraphs cited by applicant teach that chemical modifications render the construct capable of several properties and do not teach that non-nucleic acid entities confer such properties. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist for each claim limitation added in the amended claims filed on 7/13/2006. Therefore, the instant claims are accorded an effective filing date of 11/25/1997, the filing date of the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 246-252, 255, 257, 258, and 264-267 are rejected under 35 U.S.C. 102(a) as being anticipated by Pardridge et al. (Proc. Natl. Acad. Sci., Pharmacology, June 1995, Vol. 92, pages 5592-5596).

The invention of the above claims is drawn to a chemically modified nucleic acid construct, wherein said construct comprises a modified nucleotide, a nucleotide analog, or a combination of the foregoing, wherein said modified nucleotide or nucleotide analog comprises a non-nucleic acid entity that confers nuclease resistance, cell targeting, cellular localization or nuclear localization, or a combination of the foregoing, which construct when present in a cell directs the synthesis of a nucleic acid product having a

biological activity, wherein said product is chosen from antisense RNA, antisense DNA, sense RNA, ribozymes, mRNA, or a combination of these. The claims further direct that the construct be linear, circular, or branched, or that the construct be single-stranded, double stranded, partially double stranded, or triple stranded, or that the construct have a terminus which comprises a polynucleotide tail, which may be hybridized to a complementary polynucleotide sequence, or wherein the construct comprises DNA, RNA, a hybrid thereof, a chimera thereof, or a combination. The invention is further directed to modifications of the construct.

At the outset it is noted that claims 249, 255, 257, 258, 264, 265, and 267 recite limitations of elements from the broad claim, wherein said elements are stated in the alternative. Accordingly, because such elements are stated in the alternative, and because all limitations of the broad claim are read into the later depending claim, art that teaches one element is considered to reject the entire claim, even in later dependant claims which limit alternative elements that are not taught in the art, because those elements are not excluded in the claim language of the broad claim. For example, broad claim 246 recites nucleic acid constructs comprising A) a modified nucleotide, OR B) a nucleotide analog, OR C) a combination of the foregoing. Claim 255 recites the construct of claim 246, wherein at least one of said nucleotide analog or analogs have been modified on the backbone or side chain or both. However, because all claim limitations of the broad claim 246 are read into claim 255, and because claim 255 does not specifically exclude the elements of modified nucleotide of claim 246, art directed to the modified nucleotide of claim 246 is also considered to anticipate claim 255.

Pardridge et al. teach that PNAs are nucleic acid molecules with antisense effects that may prove to be effective pharmaceuticals if they can undergo transport through the brain capillary endothelial wall. Pardridge et al. teach that PNAs have a neutral backbone and that it is necessary to use delivery systems for these molecules, such as vector mediated peptide-drug delivery systems. Pardridge et al. teach an 18-mer that is antisense to the *rev* gene and is biotinylated and linked to a conjugate of streptavidin (SA) and the OX26 murine monoclonal antibody. The PNA nucleic acid construct of Pardridge et al. comprises a nucleotide analog and a non-nucleic acid entity. Pardridge et al. teach that the PNAs are analogues of DNA in which the backbone is modified and replaced with a polyamide backbone. The PNA nucleic acid constructs "directs the synthesis" of a nucleic product having biological activity because the PNA is able to bind to *rev* mRNA. Therefore, since the PNA is able to inhibit the synthesis of a nucleic product, the PNA "directs the synthesis", as instantly claimed.

The PNA of Partridge et al. is linear and single-stranded. The single-stranded PNA is considered to comprise a polynucleotide tail that is hybridized to a complementary polynucleotide sequence. The PNA is modified via attachment to biotin. The non-nucleic acid entity is the peptide nucleic acid backbone wherein the phosphate backbone is replaced with a polyamide backbone (see Materials and Methods) and are synthetic polymers, more specifically heteropolymers.

The instant specification teaches that "Nucleic acid analogues are polymers capable of binding to a complementary nucleic acid and in which these polymer backbones are other than ribo- and deoxyribose sugars and phosphate groups or in

which side chain groups are other than natural or modified bases. Examples of nucleic acid analogue polymers include peptide nucleic acids..." (see page 37, last paragraph).

Therefore, the chemically modified nucleic acid construct of Pardridge et al. anticipates the instant claims.

Claims 268-270 are rejected under 35 U.S.C. 102(a) as being anticipated by Craig et al. (WO 95/06129).

The invention of the above claims is drawn to a nucleic acid construct which when present in a cell produces a nucleic acid product, said product being bound covalently to an entity comprising a ligand in two or more locations on said construct. The construct has at least one terminus comprising a polynucleotide tail that is hybridized to a complementary polynucleotide sequence.

Craig et al. teach a complex comprising a biologically active agent, such as a nucleic acid that comprises a transcription unit encoding a RNA molecule that is capable of eliciting a biological effect, and ligands that are capable of binding to a target cell (see page 5 and 7). Craig et al. teach that the product of the transcription unit may be an RNA molecule, such as an antisense RNA molecule or a ribozyme and the ligand is any entity capable of binding to the surface of a cell, such as proteins or nucleic acids (see page 8). The ligand was bound in various positions on the construct. The construct comprises a sequence that encodes an antisense oligonucleotide, wherein the sequence has a terminus that necessarily comprises a polynucleotide tail, wherein the polynucleotide tail sequence can hybridize to a complementary sequence.

Therefore, the instant claims are anticipated by Craig et al.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is (571) 272-0755.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Amy H Bowman
Examiner
Art Unit 1635

JON E. ANGELL, PH.D.
PRIMARY EXAMINER

AHB